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EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
04/19/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/564,009	SHARIFI ET AL.	
	Examiner	Art Unit	
	KEVIN HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *February 9, 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,11 and 12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,11 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Amendments

Applicant's response and amendments, filed February 9, 2011, to the prior Office Action is acknowledged. Applicant has cancelled Claims 2, 5-10 and 13-19,

If the claims are amended, added and/or canceled in response to this Office Action, then Applicant is required to follow Amendment Practice under 37 C.F.R. §1.121 AND A CLEAN COPY OF ALL PENDING CLAIMS IS REQUESTED.

Claims 1, 3-4 and 11-12 are under consideration.

Priority

This application is a 371 of PCT/US04/22827 filed July 15, 2004. Applicant's claim for the benefit of a prior-filed application parent provisional application 60/487,409, filed on July 15, 2003 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Examiner's *Note*

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the February 9, 2011 response will be addressed to the extent that they apply to current rejection(s).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 101

1. **The prior rejection of Claims 15-19 under 35 U.S.C. 101 is withdrawn** in light of Applicant's cancellation of the claims.

Claim Rejections - 35 USC § 102

2. **The prior rejection of Claims 5, 8, 13, 15 and 17-19 under 35 U.S.C. 102(b)** as being anticipated by Scherman et al (U.S. Patent 5,945,400) **is withdrawn** in light of Applicant's cancellation of the claims.

3. **The prior rejection of Claims 5, 7-8, 13 and 15-19 under 35 U.S.C. 102(b)** as being anticipated by Colley et al (WO 99/53943; of record in IDS), as evidenced by Robbins et al

(Trends Biotechnol. 16(1):35-40, 1998) **is withdrawn** in light of Applicant's cancellation of the claims.

Claim Rejections - 35 USC § 103

4. **Claims 1 and 11 stand rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS) and Powers et al (2002; *of record).

Response to Arguments

Applicant argues that Havemann et al is not an enabling disclosure because they disclose the use of one or more growth factors to influence differentiation, survival, migration or vascularization. The laundry list of growth factors provides a myriad of possible combinations of growth factors, which Applicant calculates to be about 3.4×10^{10}.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner appreciates Applicant's demonstration of math. However, Applicant's argument is not on point. The instant claims do not require a combination of growth factors to achieve the claimed result. Further, the ordinary artisan need not take Applicant's chosen argument of growth factor combinations. The substantive issue is that Havemann et al disclose that only **one** [emphasis added] growth factor [0037] selected from the Markush Group is necessary. Pleiotrophin is clearly disclosed within the Markush Group.

A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). No undue experimentation is required. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). Havemann et al explicitly discloses that PTN is a growth factor that promotes the differentiation of mononuclear cells into endothelial cells [0066, 0072]. At the time of the instantly asserted invention (priority date of July, 2003), cell culture techniques were routinely practiced for several decades by the ordinary artisan, and it was routine in the art to apply PTN to cultured cells at various concentrations and for various

amounts of time (Powers). Furthermore, the ordinary artisan need only provide PTN to the monocytes and observe the corresponding effect.

Thus, it is unclear how the disclosure of Havemann et al directed to one growth factor is considered non-enabling.

Applicant argues that the Examiner must give meaningful consideration of the Natarajan Declaration.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner did and stated so in the prior Office Action. It's level of probative value per its content was fully considered.

Applicant argues that the claims are directed to artificially increasing the expression of pleiotrophin (PTN) in the monocytic cell by **transducing** the monocytic cell in vitro with a retrovirus expressing PTN such that the monocytic cell transdifferentiates into an endothelial cell. Applicants' claims are not directed to the use of culture conditions to induce transdifferentiation of the monocytic cell into the endothelial cell. Whether the claims exclude further steps that include a culture condition containing gangliosides, phospholipids, and glycolipids is not the issue; the Examiner is missing the point that the active step of transducing the monocytic cell in vitro with a retrovirus expressing PTN causes the monocytic cells to transdifferentiate into an endothelial cell.

Applicant's argument(s) has been fully considered, but is not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Havemann et al disclosed that the mononuclear cells may be transformed in vitro with a gene encoding an effector gene, i.e. a growth factor, to promote the endothelialization of injured vessels or angiogenesis [0032, 0047, 0075, 0191], wherein the transgene may be unrestrictedly activatable, and activation of the activation sequence is self-enhancing [0042], and wherein the transgene is encoded by a viral vector [0049]. Havemann et al do not disclose ipsis verbis that the viral vector to transfect the

mononuclear cells to be a retroviral vector; however, Havemann et al disclose that those of ordinary skill in the prior art recognize retroviral vectors are used to express an active compound [0002, 0004], and discloses the use of retroviral elements for the expression vector [0124-0125]. Thus, absent evidence to the contrary, those of ordinary skill in the art would reasonably conclude the viral vector to transfect the mononuclear cells reasonably embraces retroviral vectors.

Applicant argues that the Examiner appears to allege that Souttou adds to the disclosure that PTN is responsible for transdifferentiating monocytic cells into endothelial cells by its disclosure that PTN is an angiogenic growth factor

Applicant's argument(s) has been fully considered, but is not persuasive. Applicant appears to have mis-read or mis-interpreted the Examiner's statements. Havemann et al disclosed that the mononuclear cells may be transformed in vitro with a gene encoding an effector gene, i.e. a growth factor, to promote the endothelialization of injured vessels or angiogenesis [0032, 0047, 0075, 0191]. Havemann et al does not teach ipsis verbis that the pro-angiogenic effector transgene [0191] to encode PTN. However, at the time of the invention, Souttou et al taught that PTN is an angiogenic factor acting on endothelial cell proliferation, migration, survival, and capillary-like structure formation (pg 64, col. 1, last ¶)."

Applicant continues to argue that the Examiner has exercised impermissible hindsight in order to reject the claims, and is exercising cherry picking of particular disclosures to combine them in a way that does not reasonably flow from the combined teachings of the prior art.

Applicant's argument(s) has been fully considered, but is not persuasive. In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the Examiner has taken into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made. Havemann et al explicitly discloses that PTN is a growth factor that promotes the differentiation of mononuclear cells into endothelial cells [0066, 0072]. Havemann et al disclose the transfection of mononuclear cells with a nucleic acid construct for gene therapy, wherein the construct comprises an effector gene [0032, 0096], the effector gene being a growth factor [0047], e.g. angiogenesis growth factors.

[0191]. Those of ordinary skill in the art had long-recognized that PTN is an angiogenic growth factor, thus the specific examples of VEGF and FGF [0191] are art-recognized species within the same genus of angiogenic growth factors that embraces PTN [0037]. Havemann et al cite Vile et al [0244] demonstrating that retroviral vectors were known in the prior art. Given that Havemann et al explicitly discloses that PTN is a growth factor that promotes the differentiation of mononuclear cells into endothelial cells [0066, 0072], Havemann et al is considered to provide a reasonable teaching and/or motivation for the ordinary artisan to transduce a monocytic cell with a retroviral expression vector encoding PTN to transdifferentiate the cell into an endothelial cell because the transdifferentiation of monocytes into endothelial cells naturally flows from the expression of PTN from the expression vector. Thus, it is unclear

Applicant is respectfully reminded that obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) In the instant case, Havemann et al disclose a working example using a pro-angiogenic growth factor, VEGF or ECGF (species within the same genus of angiogenic growth factors disclosed to have the property of promoting endothelial cell differentiation from mononuclear cells [monocytes]), to transdifferentiate mononuclear cells into endothelial cells (Example 3). Thus, absent evidence to the contrary, Havemann et al provide those of ordinary skill in the art with sufficient teaching, suggestion and a reasonable expectation of success for using PTN to transdifferentiate monocytes into endothelial cells.

5. **Claim 3 stands rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS) and Powers et al (J2002; *of record), as applied to Claims 1 and 11 above, and in further view of Kume et al (2000; *of record).

Response to Arguments

Applicant argues that Kume et al do not cure the defect of Havemann et al, Souttou et al and Powers et al.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner's response to Applicant's argument(s) regarding Havemann et al, Souttou et al and Powers et al are discussed above and incorporated herein. Applicant does not contest the teachings of Kume et al as applied to the obviousness to substitute the retroviral expression vector by Havemann et al with a bicistronic retroviral expression vector as taught by Kume et al, with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

6. **Claim 4 stands rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS), Powers et al (2002; *of record) and Kume et al (2000; *of record), as applied to Claims 1, 3 and 11 above, and in further view of Pufe et al (2003; *of record in IDS), Howett et al (*of record) and Eslami et al (2001; *of record).

Response to Arguments

Applicant argues that Pufe et al, Howett et al and Eslami et al do not cure the defect of Havemann et al, Souttou et al, Powers et al and Kume et al.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner's response to Applicant's argument(s) regarding Havemann et al, Souttou et al, Powers et al and Kume et al are discussed above and incorporated herein. Applicant does not contest the teachings of Pufe et al, Howett et al and Eslami et al as applied to the obviousness to substitute a first mononuclear/monocyte cell with a second monocyte cell, specifically THP-1, with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

7. **Claim 12 stands rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS), Powers et al (2002; *of record), Kume et al (2000; *of record), Pufe et al (2003; *of record in IDS), Howett et al (*of record) and Eslami et al (2001; *of record), as applied to Claims 1, 3-4 and 11 above, and in further view of Kawamoto et al (Circulation 103:634-637, 2001).

Response to Arguments

Applicant argues that Kawamoto et al do not cure the defect of Havemann et al, Souttou et al, Powers et al, Kume et al, Pufe et al, Howett et al and Eslami et al.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner's response to Applicant's argument(s) regarding Havemann et al, Souttou et al, Powers et al, Kume et al, Pufe et al, Howett et al and Eslami et al are discussed above and incorporated herein.

Applicant does not contest the teachings of Kawamoto et al as applied to the obviousness to substitute substitute the in vitro transdifferentiation step as taught by Havemann et al with an in vivo transdifferentiation step, with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention, the motivation being that PTN has been repeatedly reported to induce the proliferation of endothelial cells and is an art-recognized angiogenic factor and Kawamoto et al successfully demonstrated the ability of monocytes to transdifferentiate into endothelial cells and incorporate at sites of neovascularization when implanted in vivo, thereby improving blood flow from an ischemic event.

8. **The prior rejection of Claims 5, 13, 15 and 18 under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS) and Powers et al (2002; *of record) **is withdrawn** in light of Applicant's cancellation of the claims.

9. **The prior rejection of Claims 7 and 16 under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS) and Powers

et al (J2002; *of record), as applied to Claims 5, 13, 15 and 18 above, and in further view of Kume et al (2000; *of record) **is withdrawn** in light of Applicant's cancellation of the claims.

10. **The prior rejection of Claims 8 and 17 under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS), Powers et al (2002; *of record) and Kume et al (2000; *of record), as applied to Claims 5, 7, 13, 15-16 and 18 above, and in further view of Pufe et al (2003; *of record in IDS), Howett et al (*of record) and Eslami et al (2001; *of record) **is withdrawn** in light of Applicant's cancellation of the claims.

11. **The prior rejection of Claim 19 under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS), Powers et al (2002; *of record), Kume et al (2000; *of record), Pufe et al (2003; *of record in IDS), Howett et al (*of record) and Eslami et al (2001; *of record), as applied to Claims 5, 7-8, 13 and 15-18 above, and in further view of Kawamoto et al (Circulation 103:634-637, 2001) **is withdrawn** in light of Applicant's cancellation of the claims.

Conclusion

12. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/
Primary Examiner, Art Unit 1633